19. (Amended) The thrombin preparation as claimed in claim 18, which additionally comprises a soluble calcium salt, sodium chloride as stabilizer, a buffer substance, and further comprises at least one of

a sugar,

a sugar alcohol,

an amino acid,

a salt of a mono- or polycarboxylic acid, or

a salt of a mono- or polyhydroxycarboxylic acid,

wherein the thrombin preparation is stable in the liquid state.

REMARKS

Status of the Claims

Claims 18-38 are pending in this application and claims 18, 19, and 35-38 are presently under examination. Applicants have amended claim 19 to clarify that sodium chloride is employed as stabilizer.

Applicants respectfully request the entry of this Amendment under 37 C.F.R. § 1.116, placing claims 18, 19, and 35-38 in condition for allowance. Applicants submit that the proposed amendment should allow for immediate action because it does not raise new issues or require any additional search of the art. The entry of this Amendment would also place the application in better form for appeal, should Office continue to dispute the patentability of the pending claims.

Restriction Requirement

Applicants acknowledge that the Office has made the restriction of claims 20-34 final. However, Applicants note that claims 32 and 33 depend from claims 18 and 19 and recite a method of using the thrombin preparation of those claims. Therefore, upon allowance of claims 18 and 19, Applicants respectfully request that claims 32 and 33 be rejoined in accordance with 37 C.F.R. § 1.141 and M.P.E.P. § 821.04.

Objection to the Specification

The Office maintained the objection to the lack of headings in the specification, citing 37 C.F.R. § 1.77.

The present application is based on German Application No. DE 100 12 732.0, which does not contain subject headings. Applicants demur from adding these headings because they are not required by statute. Moreover, characterization of certain parts of the specification as "Field of the Invention" or "Background of the Invention" can lead to inadvertent admissions against interest when an application has not been originally structured to accommodate such divisions, as here. For example, an application originally structured without headings may interweave discussions of the prior art with comparisons to the claimed invention, upon which the inventors seek to rely for support. If such a segment of the specification were to be labeled "Background of the Invention" or "Description of the Related Art," an applicant might be prevented from relying on it in support of the claims. To avoid possible error, Applicants request

Rejection of claims 18 and 35-37 under 35 U.S.C. § 102(e)

The Office maintained the rejection of claims 18 and 35-37, asserting that they are anticipated by Hanada et al. ("Hanada"; U.S. Patent No. 5,945,103). Applicants respectfully traverse this rejection.

Claim 18 recites: "A thrombin preparation comprising thrombin and a noncovalently binding inhibitor of thrombin activity as stabilizer, wherein the thrombin preparation is suitable for therapeutic purposes." Therefore, claim 18, as well as claims 35-37 which depend from it, cannot read on every solution containing thrombin and a "noncovalently binding inhibitor of thrombin activity as stabilizer," but only those that are also "suitable for therapeutic purposes." In other words, claims 18 and 35-37 do not read on solutions that cannot be directly administered to a patient as a tissue glue or as an agent for local stoppage of bleeding, for example.

The only composition of Hanada that can be compared to claims 18 and 35-37 is the one mentioned at col. 4, lines 13-37, in which trialkylphosphate treatment of a thrombin-containing solution is carried out. This is the only thrombin solution that Hanada mentions that may include both thrombin and a "noncovalent inhibitor of thrombin activity," such as a benzamidine. While "Inventive Example 1" of Hanada also describes trialkylphosphate treatment, no "noncovalent inhibitor of thrombin activity" is employed there. (See Hanada at col. 5, lines 25-50.)

Hanada does not state that the trialkylphosphate treatment solution is "suitable for therapeutic purposes," as required by claims 18 and 35-37. Thus, in the present

inherency, the composition of the prior art must necessarily function in accordance with or include all of the claimed limitations. As the Federal Circuit has explained,

"Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Contintental Can Co. USA, Inc. v. Monsanto Co.,* 948 F.2d 1264, 1268-9, 20 U.S.P.Q.2d 1746, 1749 (Fed. Cir. 1991.) To support an anticipation rejection based on inherency, the Office must provide factual and technical grounds establishing that the inherent feature necessarily flows from the teachings of the cited art. *See In re Oelrich*, 666 F.2d 578,581, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981); *Ex parte Levy*, 17 U.S.P.Q.2d 1461, 1464 (Bd. Pat. App. & Int. 1990); *see also* M.P.E.P. § 2131.01 (III).

Applicants submit that the Office has failed to meet its burden under the substantial evidence standard to support its assertion that this trialkylphosphate treatment solution is inherently and necessarily "suitable for therapeutic use." *In re Zurko*, 258 F.3d 1379, 59 U.S.P.Q.2d 1693 (Fed. Cir. 2001). Instead, the Office merely stated that "[t]he same composition as that which is claimed is taught in Hanada." (Office Action at page 3.) Such conclusory statements are not sufficient to support a *prima facie* case. *See In re Lee*, 277 F.3d 1338, 61 U.S.P.Q.2d 1430 (Fed. Cir. 2002). The burden is on the Office to present factually supported reasoning explaining why the Hanada solution inherently and necessarily teaches all of the elements of claim 18 as well as each of claims 35-37, including the element of therapeutic suitability and the requirement of claim 37 that "after 12 months of storage at 20-25 °C, the thrombin maintains at least 70% of its original level of activity." Without such evidence, the present rejection does not present a *prima facie* case of anticipation.

that the Hanada solution is not therapeutically suitable. Trialkylphosphates, such as tri-

(n-butyl) phosphate, are organic solvents used for disrupting biological membranes, such as those of enveloped viruses and mammalian cells. In fact, disrupting viral membranes was the purpose of Hanada's trialkylphosphate treatment. (See also U.S. Patent No. 4,540,573, cited in Hanada at col. 4., and U.S. Patent No. 3,962,421; both submitted herewith as Exhibits A and B.) These solvents are also skin irritants, perhaps due to their ability to disrupt lipid membranes. (See the attached chemical safety information on tri-(n-butyl) phosphate; Exhibit C.) These properties indicate that a solution containing a level of trialkylphosphate effective to disrupt viral membranes, as described by Hanada, is not therapeutically suitable. Such a solution might damage a patient's cells and irritate the skin it was intended to heal.

Further, the fact that Hanada conducts a buffer-exchange chromatography procedure immediately following the trialkylphoshate treatment in the examples also indicates that the chemicals present in the trialkylphosphate solution may not be therapeutically compatible. (Col. 5, lines 25-50; and see U.S. Patent No. 4,540,573 at col. 9, lines 19-24, and U.S. Patent No. 3,962,421 at col. 5, lines 1-5, which point out that trialkylphosphate should be removed or heavily diluted following the treatment.)

For all of these reasons, the solution described at col. 4 of Hanada is not necessarily "suitable for therapeutic purposes," and cannot anticipate claims 18 and 35-37. Thus, Applicants request the withdrawal of this rejection.

Rejection of claim 38 under 35 U.S.C. § 102(e), or, alternatively, under 35 U.S.C. § 103(a)

Hanada, noting that Hanada does not give the pH of the solution. (Office Action at page

3.) Applicants respectfully traverse the anticipation rejection under § 102(e) on the same grounds as that described above relating to claims 18 and 35-37. The obviousness rejection is discussed below.

Rejection of claims 18, 19, and 35-38 under 35 U.S.C. § 103(a)

The Office also maintained the rejection of claims 18, 19, and 35-38 as allegedly obvious over Hanada in view of Brezniak et al. ("Brezniak"; *Blood Coagulation and Fibrinolysis*, 5: 847-8 (1994)) and Altshuler et al. ("Altshuler"; U.S. Patent No. 4,363,319). Applicants respectfully traverse this rejection.

The Office asserted that Hanada teaches the elements of claim 18, as well as the amino acids, sodium chloride, and sugar alcohols recited in claim 19. The Office relied on Brezniak and Altshuler for a teaching of thrombin in combination with a soluble calcium salt. Neither Brezniak nor Altshuler describes "noncovalent inhibitors of thrombin activity."

Regarding Hanada's teachings, the Office merely stated that "[t]he same composition as that which is claimed is taught in Hanada." (Office Action at pages 3 and 4.) As Applicants have remarked, however, Hanada does not teach a composition containing any "noncovalent inhibitor of thrombin activity" that is also "suitable for therapeutic use." The inhibitor may only be added during trialkylphosphate treatment. (Col. 4.)

Again, the only support the Office provided for this rejection is a conclusory

solution of Hanada is, or could be, therapeutically suitable. Indeed, the Federal Circuit

has recently pointed out that the Office "cannot rely on conclusory statements" in establishing a *prima facie* case of obviousness, "but must set forth the rationale on which it relies," and that "[t]his precedent has been reinforced in myriad decisions, and cannot be dispensed with." *In re Lee*, 277 F.3d at 1345, 61 U.S.P.Q.2d at 1435 (citations omitted).

Moreover, the therapeutically useful composition described in Hanada is a pure thrombin solution obtained after all of the reagents used in trialkylphosphate treatment have been removed and further processing steps have been performed. (Col. 5, lines 25-50.) Therefore, Hanada does not provide one of ordinary skill in the art with any motivation to add a "noncovalent inhibitor of thrombin activity" to a thrombin preparation intended for therapeutic use. Because Brezniak and Altshuler do not address these inhibitors at all, they do not remedy this critical deficiency.

Because one of skill in the art applying the teachings of Hanada, Brezniak, and Altshuler, would not arrive at Applicants' claimed thrombin preparation, Applicants respectfully request the withdrawal of this rejection.

CONCLUSION

In view of the foregoing remarks, Applicants submit that claims 18, 19, and 35-38, as amended, are in condition for allowance. Applicants therefore request the entry of this Amendment, the reconsideration and reexamination of the application, and the timely allowance of the pending claims.

$400.00.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: November 19, 2002

By: _____
Elizabeth A. Doherty
Reg. No. 50,894

APPENDIX TO AMENDMENT OF NOVEMBER 19, 2002

Version showing Changes Made

Amendments to the Claims:

19. (Amended) The thrombin preparation as claimed in claim 18, which additionally comprises a soluble calcium salt, [and] sodium chloride as stabilizer[s], a buffer substance, and further comprises at least one of

a sugar,

a sugar alcohol,

an amino acid,

a salt of a mono- or polycarboxylic acid, or

a salt of a mono- or polyhydroxycarboxylic acid,

wherein the thrombin preparation is stable in the liquid state.

NTP CHEMICAL REPOSITORY
TRIBUTYL PHOSPHATE

-IDENTIFIERS
==========

*CATALOG ID NUMBER: 002085

*CAS NUMBER: 126-73-8

*BASE CHEMICAL NAME: TRIBUTYLPHOSPHATE

*PRIMARY NAME: TRIBUTYL PHOSPHATE

*CHEMICAL FORMULA: C12H27O4P

*STRUCTURAL FORMULA: (CH3CH2CH2CH2O)3PO

*WLN: Not available

*SYNONYMS:
BUTYL PHOSPHATE, TRI-
CELLUPHOS 4
TBP
PHOSPHORIC ACID, TRIBUTYL ESTER
TRI-N-BUTYL PHOSPHATE

-PHYSICAL CHEMICAL DATA
=======================

*PHYSICAL DESCRIPTION: LITERATURE: Colorless to pale yellow liquid
REPOSITORY: Clear, pale-yellow liquid

*MOLECULAR WEIGHT: 266.36

*SPECIFIC GRAVITY: 0.9727 @ 25/4 C [017]

*DENSITY: Not available

*MP (DEG C): <-80 C [031,062,421]

*BP (DEG C): 289 C [017,031]

*SOLUBILITIES:
WATER : <1 mg/mL @ 20.5 C (RAD)

DMSO : >=100 mg/mL @ 20.5 C (RAD)

95% ETHANOL : >=100 mg/mL @ 20.5 C (RAD)

METHANOL : Not available

-OTHER SOLVENTS
Ether Soluble [017]

Benzene: Soluble [017]
Common organic solvents: Miscible [421]

*VOLATILITY:
Vapor pressure: 13.7 mm Hg @ 20 C [058]
Vapor density : 9.20 [042]

*FLAMMABILITY(FLASH POINT):
This chemical has a flash point of 146 C (295 F) [042,062,421]. It is combustible. Fires involving this material can be controlled with a dry chemical, carbon dioxide or Halon extinguisher. The autoignition temperature of this compound is >482 C (>900 F) [058].

*UEL: Not available LEL: Not available

*REACTIVITY:
This compound is incompatible with strong oxidizing agents and strong bases [269]. It will attack some forms of plastics and rubber [102].

*STABILITY:
This material hydrolyzes slowly under wet alkaline conditions [058]. Solutions of this chemical in water, DMSO, 95% ethanol or acetone should be stable for 24 hours under normal lab conditions (RAD).

*OTHER PHYSICAL DATA:
Refractive index: 1.4224 @ 25 C
Viscosity: 4.5 centipoise @ 25 C
Boiling point: 160-162 C @ 15 mm Hg [017]; 177-178 C @ 27 mm Hg [031]
Boiling point: 180-183 C @ 22 mm Hg [058]

-TOXICITY
========

*NIOSH REGISTRY NUMBER: TC7700000

*TOXICITY: **(abbreviations)**

typ. dose	mode	specie	amount	units	other
LD50	orl	rat	3000	mg/kg	
LD50	ipr	rat	251	mg/kg	
LDLo	ivn	rat	100	mg/kg	
LD50	orl	mus	1189	mg/kg	
LC50	ihl	mus	1300	mg/m3	
LDLo	ipr	mus	63	mg/kg	
LDLo	scu	mus	3	gm/kg	
LCLo	ihl	cat	24510	mg/m3/5H	

*AQTX/TLM96: Not available

*SAX TOXICITY EVALUATION:
THR: A skin and eye irritant. HIGH via intravenous and intraperitoneal routes. MODERATE via oral route. It has effects on the central nervous system in humans. It is irritating to mucous membranes.

Not available

*TERATOGENICITY:
Reproductive Effects Data:
TDLo: orl-rat 12600 mg/kg (63D male)

*STANDARDS, REGULATIONS & RECOMMENDATIONS:
OSHA: Federal Register (1/19/89) and 29 CFR 1910.1000 Subpart Z
Transitional Limit: PEL-TWA 5 mg/m3 [610]
Final Limit: PEL-TWA 0.2 ppm [610]
ACGIH: TLV-TWA 0.2 ppm [015,413,421,610]
NIOSH Criteria Document: None
NFPA Hazard Rating: Health (H): 2
Flammability (F): 1
Reactivity (R): 0
H2: Materials hazardous to health, but areas may be entered freely with full-faced mask self-contained breathing apparatus which provides eye protection (see NFPA for details).
F1: Materials that must be preheated before ignition can occur (see NFPA for details).
R0: Materials which are normally stable even under fire exposure conditions and which are not reactive with water (see NFPA for details).

*OTHER TOXICITY DATA:
Skin and Eye Irritation:
skn-rbt 10 mg/24H open
eye-rbt 97 mg
Status: "NIOSH Manual of Analytical Methods" Vol 3
"NIOSH Manual of Analytical Methods" to be revised by June, 1985
Reported in EPA TSCA Inventory, 1983
Meets criteria for proposed OSHA Medical Records Rule

-OTHER DATA (Regulatory)
==========

*PROPER SHIPPING NAME (IATA): Not restricted

*UN/ID NUMBER:

*HAZARD CLASS: SUBSIDIARY RISK: PACKING GROUP:

*LABELS REQUIRED:

*PACKAGING: PASSENGER: PKG. INSTR.: MAXIMUM QUANTITY:
CARGO : PKG. INSTR.: MAXIMUM QUANTITY:

*SPECIAL PROVISIONS:

*USES:
Plasticizer for cellulose esters; lacquers; plastic and vinyl resins; heat exchange medium; solvent extraction of metal ions from solution of reactor products; solvent for nitrocellulose and cellulose acetate; pigment grinding assistant; antifoam agent; and dielectric.

*ACUTE/CHRONIC HAZARDS:
This compound is a mild **CHOLINESTERASE INHIBITOR** [151]. It is a mucous membrane irritant [031]. It is a skin irritant and is narcotic [421]. When heated to decomposition it emits toxic fumes of POx [042].

*MINIMUM PROTECTIVE CLOTHING:
If Tyvek-type disposable protective clothing is not worn during handling of this chemical, wear disposable Tyvek-type sleeves taped to your gloves.

*RECOMMENDED GLOVE MATERIALS:
Recommended Glove Type For Use With Neat (Undiluted) Chemical:
Recommendations based on permeation test results are made for handling the neat (undiluted) chemical. If this chemical makes direct contact with your glove, or if a tear, puncture or hole develops, replace them at once.

Suggested Glove Type(s) (RAD): No information available

*RECOMMENDED RESPIRATOR:
Where the neat test chemical is weighed and diluted, wear a NIOSH-approved half face respirator equipped with an organic vapor/acid gas cartridge (specific for organic vapors, HCl, acid gas and SO2) with a dust/mist filter.

*OTHER: Not available

*STORAGE PRECAUTIONS:
You should store this chemical under ambient temperatures, and keep it away from oxidizing materials.

*SPILLS AND LEAKAGE:
If you spill this chemical, FIRST REMOVE ALL SOURCES OF IGNITION. Then, use absorbent paper to pick up all liquid spill material. Your contaminated clothing and absorbent paper should be sealed in a vapor-tight plastic bag for eventual disposal. Solvent wash all contaminated surfaces with 60-70% ethanol followed by washing with a soap and water solution. Do not reenter the contaminated area until the Safety Officer (or other responsible person) has verified that the area has been properly cleaned.

*DISPOSAL AND WASTE TREATMENT: Not available

-EMERGENCY PROCEDURES
==========

*SKIN CONTACT:
IMMEDIATELY flood affected skin with water while removing and isolating all contaminated clothing. Gently wash all affected skin areas thoroughly with soap and water.
IMMEDIATELY call a hospital or poison control center even if no symptoms (such as redness or irritation) develop.
IMMEDIATELY transport the victim to a hospital for treatment after washing the affected areas.

hospital even if no symptoms (such as wheezing, coughing, shortness of breath, or burning in the mouth, throat, or chest) develop.
Provide proper respiratory protection to rescuers entering an unknown

atmosphere. Whenever possible, Self-Contained Breathing Apparatus (SCBA) should be used; if not available, use a level of protection greater than or equal to that advised under Respirator Recommendation.

*EYE CONTACT:

First check the victim for contact lenses and remove if present. Flush victim's eyes with water or normal saline solution for 20 to 30 minutes while simultaneously calling a hospital or poison control center.

Do not put any ointments, oils, or medication in the victim's eyes without specific instructions from a physician.

IMMEDIATELY transport the victim after flushing eyes to a hospital even if no symptoms (such as redness or irritation) develop.

*INGESTION:

DO NOT INDUCE VOMITING. If the victim is conscious and not convulsing, administer a slurry of activated charcoal in water and simultaneously call a hospital or poison control center. IMMEDIATELY transport the victim to a hospital.

If the victim is convulsing or unconscious, do not give anything by mouth, ensure that the victim's airway is open and lay the victim on his/her side with the head lower than the body. DO NOT INDUCE VOMITING. IMMEDIATELY transport the victim to a hospital.

*SYMPTOMS:

Symptoms of acute exposure to this compound may include headaches, tremors, drowsiness, convulsions, hypnosis and anesthesia [042]. It can cause weakness, dyspnea, coma and pulmonary edema [151]. It can also cause nausea [058]. It is irritating to the mucous membranes [031]. It is also irritating to the skin [421].

-SOURCES

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